Comply regarding sequence listings. Further, the items listed on the Notice to Comply regarding sequence listings are enclosed herewith as separate enclosures. No new matter has been added. Reconsideration is respectfully requested.

Claims 1-29 and 50-84 are canceled, without prejudice, for being drawn to a non-elected invention. Applicant reserves the right to file a continuation application with non-elected Claims 1-29 and 50-84 during the pendency of the present application.

The abstract of the disclosure was objected to for containing more than the 150 word limit. Applicant has amended the Abstract to limit the word count accordingly. Consideration of the amended Abstract is respectfully requested.

Applicant has amended the specification at page 4, lines 11-17 to fix a typographical error on line 15 therein. Consideration of the amended Specification is respectfully requested.

Further, Applicant has amended the specification at page 24, Table 1, to add a SEQ ID NO column and number for each of the sequences listed in Table 1 in compliance with 37 CFR 1.821(d). The SEQ ID NOs correspond to the SEQ ID NOs of the enclosed Sequence Listing. Consideration of the amended Table 1 is respectfully requested.

Claims 30-49 were rejected under 35 USC 112, second paragraph, as being indefinite. The Examiner contended that Claims 30-49 were indefinite because Claim 30 was drawn to a method of making an array, but the claim does not recite method steps of array making. The Examiner further contended that the claims were indefinite because it was unclear whether the microarray comprises the control and the test probes. The Examiner suggested that Claim 30 be amended to recite positive and active steps for making a microarray, e.g., attaching probes at a location on a surface and referred to page 9, lines 12-20.

Applicant appreciates the Examiner's suggestion and has amended Claim 30 to clarify the meaning of "providing". Claim 30 now recites that the control probes are provided by attaching the control probe to the surface in the array pattern. The oligomer test probes are provided by attaching the oligomer test probe in the array pattern. Claims 31-49 are directed to different embodiments of the attachment of the probes. It is respectfully submitted that amended Claim 30 is clear and recites positive steps of making an array. Consideration of this amendment is respectfully requested.

With respect to the Examiner's contention that it was unclear whether the microarray comprises the control and the test probes, Applicant respectfully submits that Claim 30, as amended herein, recites that both a control probe and an oligomer test probe are provided, such as by attaching, to an array pattern of features on the microarray substrate, such that the features comprise the control probe and the oligomer test probe. Consideration of this amendment is respectfully requested.

The Examiner further contended that Claims 30-49 were indefinite because Claim 30 recites 'the control probe being associated with a control label', and "being associated with" was a non-specific relational phrase, making the relationship between the control probe and the control label undefined. The Examiner suggested that Claim 30 be amended to define the relationship e.g., by replacing "associated with" with "directly or indirectly attached".

Again, Applicant appreciates the Examiner's suggestion and has amended Claim 30 to recite 'directly or indirectly labeled' instead of 'being associated with'. Consideration of this amendment is respectfully requested.

The Examiner further contended that Claims 30-49 were indefinite because Claims 30, 34 and 38 recite "each feature location", which lacks proper antecedent basis. The Examiner suggested that Claim 30 be amended to provide proper antecedent basis, e.g., by inserting "each feature having a location" after "features" on line 3, or with respect to the rejection of Claim 38, otherwise deleting "location" in Claim 38.

Applicant appreciates the Examiner's suggestions and proposes deleting "location" from Claims 30, 34 and 38. Since the word 'feature' is defined as a location or 'locus', in the specification at page 2, lines 1-2, and page 6, lines 18-20, both Applicant's "feature location" and the Examiner's suggested amendment "each feature having a location" seem redundant. Applicant respectfully requests consideration of this amendment to delete "each feature location" and "each feature" and substitute therefor 'the features' to overcome lack of antecedent basis with respect to Claims 30, 34 and 38. Further accordingly, Claims 31, 32, 33 and 36 were amended to substitute "the features" for "each feature".

The Examiner further contended that Claims 31-33 were each indefinite for reciting "the surface within each feature", because the phrase lacked proper antecedent basis. The Examiner suggested that Claims 31-33 be amended to provide correct antecedent basis, e.g., by replacing "the" with "a".

Applicant appreciates the Examiner's suggestion, but would like to point out that "the surface" refers back to "a surface of the substrate" in Claim 30. Therefore, "the surface" means the surface ***of the substrate*** within the features. Applicant believes that this recitation is proper. However, Applicant has added 'of the substrate' to Claims 31-33 to clarify this point for the Examiner. Reconsideration and withdrawal of the rejection of Claims 31-33 for the contended lack of antecedence are respectfully requested.

The Examiner further contended that Claims 32-34 and 36 were each indefinite for the recitation "indirectly associating the control label" because "associating" was a non-specific relational term. The Examiner suggested that Claims 32-34 and 36 each be amended to define the relationship, e.g., by replacing "associating" with "directly or indirectly attaching", and cited page 7, lines 5-20.

Applicant appreciates the Examiner's suggestion and has amended Claims 32-34 and 36 to recite 'indirectly labeling' instead of 'indirectly associating'.

The Examiner further contended that Claim 34 was indefinite for reciting "the labeled control target material", because the recitation lacked proper antecedent basis. The Examiner suggested that Claim 34 be amended to provide correct antecedent basis, e.g., by replacing "control" with "control-specific".

Applicant appreciates the Examiner's suggestion and has amended Claim 34 to recite 'the labeled control-specific target material' instead of 'the labeled control target material'.

In light of the above remarks, reconsideration and withdrawal of the rejection of Claims 30-49, as amended herein, under 35 USC 112, second paragraph, are respectfully requested.

While it is expected that these amendments overcome the rejection of Claims 30-49 under 35 USC 112, second paragraph, Applicant respectfully submits that the amendments to Claims 30-34, 36 and 38 are made to correct the form of the claims and are not made for a substantial reason related to patentability, and more importantly, that these amendments do not in any way narrow the scope of any element in any of Claims 30-49.

Claims 30-41 and 44-48 were rejected under 35 USC 102(b) as being anticipated by Lockhart et al., WO 97/27317, published 31 July 1997 ('27317). With respect to Claim 30, the Examiner contended that Lockhart et al. disclose a method of making microarray, as claimed in Claim 30. The Examiner referred to page 71, lines 1-8 and Figure 13a of Lockhart et al. ('27317) for support of this rejection. It appears that the Examiner has contended that the constant region and the variable region of the oligonucleotide probe used in the probe oligonucleotide/ligation reaction system of Lockhart et al. ('27317) are the same as Applicant's claimed control probe and test probe, respectively. It further appears that the Examiner has contended that a ligatable oligonucleotide having a label B at one end, which is ligated to the variable region at ligation site B, disclosed by Lockhart et al., was the same as Applicant's control probe being associated with a control label. The Examiner referenced Figure 13a "label b" of Lockhart et al. Applicant respectfully traverses this rejection.

The present invention is directed to a method of making a microarray that has enhanced feature detectability. The method of making the microarray comprises providing a control probe in an array pattern of features, and separately providing an oligonucleotide test probe to the features. The control probe is associated with a control label, such that after a hybridization assay and/or during scanning and detection of signals, the control probe and the associated control label within the features provide a reference for the location of the features. In this method of making a microarray, advantageously the positions or locations of the features on the array are known, i.e., detection of the features is enhanced, using the control probes. As such, reliance on the intensity of a hybridized test probe to determine or confirm the position of the features is reduced. In addition or alternatively, reliance on the placement accuracy of the deposition equipment used to place the control probe and the test probe is reduced.

Lockhart et al. ('27317) disclose on page 70, lines 24-31, that ligation reactions can be used to discriminate between fully complementary hybrids and those that differ by one or more base pairs, particularly in cases where the mismatch is near the 5' terminus of the probe oligonucleotide. Also, Lockhart et al. disclose therein that use of a ligation reaction in signal detection increases the stability of the hybrid duplex, improves hybridization specificity, especially for shorter probe oligonucleotides (e.g., 5 to 12-mers), and optionally, provides additional sequence information. Lockhart et al. fail to disclose or suggest therein that the probes, the probe regions or even the ligation reactions are used to provide feature position determination or confirmation, such that feature detection is enhanced.

Claim 30 recites making a microarray with enhanced feature detectability in the preamble thereof, as originally filed. However, Applicant has further amended Claim 30 to emphasize that the control probes enhance detection of the features without interfering with oligomer test probe hybridization. It is respectfully submitted that not only are Lockhart et al. silent on making a microarray with enhanced feature detectability, but also fail to disclose making the microarray using control probes with the test probes on the array, as presently claimed. In particular, the constant region of

the oligonucleotide probe disclosed by Lockhart et al. is not a control probe, as is known in the art, and especially as presently claimed.

For example, at page 71, lines 1-8 of Lockhart et al. ('27317), to which the Examiner referred for the rejection of Claim 30, Lockhart et al. disclose various components for use of ligation reaction(s) in combination with generic difference screening arrays. Lockhart et al. describe generic difference screening starting on page 31, for example. At page 71, lines 1-8, Lockhart et al. disclose a probe oligonucleotide/ligation reaction system that includes an array of oligonucleotide probes. The oligonucleotide probes can be randomly selected, haphazardly selected, composition biased, inclusive of all possible oligonucleotides of a particular length, and so forth. The oligonucleotide probes ***optionally*** comprise a constant region. The constant region is predetermined and has substantially the same sequence for substantially all of the probe oligonucleotides on the array. (Emphasis is added for the Examiner's convenience.)

The control probe disclosed and claimed by Applicant is not ***optional***, as Lockhart et al. has disclosed for the constant region of the oligonucleotide probe. The control probe of the present invention provides the enhanced feature detectability and therefore, is always present, not optionally present.

At page 71, lines 9-14 of Lockhart et al. ('27317), Lockhart et al. disclose that the oligonucleotide probes also preferably comprise a variable region, when the optional constant region is provided. The variable region is the randomly or otherwise selected sequence. In Figure 13a, Lockhart et al. illustrate an oligonucleotide probe having the constant region adjacent to an end of the probe (3' terminus) that is attached to the solid support, and having the variable region adjacent to an opposite end of the probe (5' terminus). When both the constant region and the variable region are present, the system further comprises a sample nucleic acid that hybridizes to the variable region of the oligonucleotide probe, and ***optionally*** hybridizes to the constant region as well.

For the purposes of the present invention, a control probe, as is known in the art, does not interfere with an assay, but instead provides a reference or a standard. In accordance with the present invention, the control probe does not interfere with the oligomer test probe hybridization. Amended Claim 30 clarifies this point. Therefore, contrary to that disclosed by Lockhart et al., a sample nucleic acid under test that hybridizes to the oligomer test probe does not ***optionally*** hybridize to the control probe as well, according to the present invention.

At page 71, line 29 to page 72, line 2 of Lockhart et al. ('27317), Lockhart et al. disclose that the various components of the probe oligonucleotide/ligation reaction system can be combined in a variety of ways to increase the stability of the hybrid duplex, and/or improve hybridization specificity, and/or provide sequence information, as mentioned above with respect to page 70. The variety of uses are then described in further detail starting at page 72, line 14 to page 83, line 27. In none of these uses do Lockhart et al. disclose or suggest using the ligation reaction system or the constant or variable regions of the probe oligonucleotide to enhance feature detection on the microarray or using the constant region as a control.

It is respectfully submitted that an anticipation determination is viewed from one of ordinary skill in the art. It is further respectfully submitted that the disclosure of Lockhart et al. ('27317), especially that pointed to by the Examiner at page 71, is different enough from the claimed invention as viewed by a person of ordinary skill in the field of the invention (*Scripps Clinic & Research Found. v. Genentech Inc.*, 927 F.2d 1565, 18 U.S.P.Q.2d 1001 (Fed. Cir. 1991)), such that Lockhart et al. fail to enable and describe the claimed invention sufficiently to have placed it in possession of the person of ordinary skill in the art (*In re Paulsen*, 30 F.3d 1475, 1478, 31 U.S.P.Q.2d 1671, 1673 (Fed. Cir. 1994)).

For example, Lockhart et al. ('27317) disclose two regions of an intact oligonucleotide probe, while Applicant separately claims two probes, one being a control probe and the other being an oligonucleotide test probe, each being separately provided to the microarray in the method of making. Further, Lockhart et al. disclose

that the oligonucleotide probe optionally comprises a constant region, while the claimed control probe of the present invention is not optional. Still further, Lockhart et al. disclose a ligatable oligonucleotide having a label B for ligating to the variable region of the intact oligonucleotide probe, while Applicant disclose that the control probe is associated with a control label, such as by direct or indirect labeling of the control probe. Moreover, Lockhart et al. do not even disclose or suggest using the ligation reaction system for enhanced feature position detection. Applicant uses the control signal from the control probe to detect the actual feature positions on the array independently of other detected signals.

Therefore, one skilled in the art, having the benefit of the teachings of Lockhart et al. ('27317), would not be in possession of the present invention. In order for anticipation to be found, a single prior art reference must disclose each and every limitation of the claimed invention (*In re Paulsen*, *supra* at 1673) as arranged in the claim (*Lindemann Maschinenfabrik GmbH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 221 U.S.P.Q. 481 (Fed. Cir. 1984)) in order to maintain an anticipation rejection.

In light of the above, reconsideration and withdrawal of the 35 USC 102(b) rejection of Claim 30 are respectfully requested.

With respect to Claim 31, the Examiner contented that Lockhart et al. disclose the method of the present invention where one end of the control probe is added to the substrate and the control probe is directly labeled with a control label, as claimed in Applicant's Claim 31. The Examiner referred to page 72, lines 23-31 and Figure 13b of Lockhart et al. ('27317) for support of this contention. Applicant also traverses this rejection.

At page 72, starting on line 14 of Lockhart et al. ('27317), Lockhart et al. disclose ligation reactions to discriminate mismatches at probe termini, target termini or both. Lockhart et al. refer to Figure 13b for the purpose of illustrating a simple ligation reaction that discriminated mismatches at or near the terminus of the probe oligonucleotide. In fact, at page 73, lines 1-30 and illustrated in Figure 13b, Lockhart

et al. disclose that the ligation reaction of the labeled, ligatable probes to the phosphorylated 5' end of the oligonucleotide probes on the substrate will occur, in the presence of the ligase, predominately when the target:oligonucleotide hybrid has formed with a correct base-pairing near the 5' end and where there is a suitable 3' overhang of the target nucleic acid to serve as a template for hybridization and ligation. The method primarily discriminates mismatches at or near the 5' terminus of the surface bound probe oligonucleotide and does little to discriminate mismatches at or near the 5' terminus of the target nucleic acid.

Contrary to that contended by the Examiner, at page 71, lines 23-31 and illustrated in Figure 13b of Lockhart et al. ('27317), Lockhart et al. do not disclose attaching one end of a control probe to the surface of the substrate. Instead, Lockhart et al. disclose attaching one end of a probe oligonucleotide to the surface of the substrate. The probe oligonucleotide is illustrated and described as being hybridized with the target nucleic acid sample. As mentioned above, in accordance with the invention, a control probe does not hybridize with the target nucleic acid sample, or interfere with the hybridization of the test probe oligonucleotide. Further, Lockhart et al. do not disclose directly labeling a control probe with a control label. Instead, Lockhart et al. disclose directly labeling the probe oligonucleotide via ligation of a labeled, ligatable oligonucleotide to the 5' terminus of the probe oligonucleotide, while the 3' terminus is attached to the substrate surface.

The Examiner pointed out that the claims are given the broadest reasonable interpretation consistent with the broad claim language "directly labeling" and that the specification does not define "directly labeling". Therefore, ligation labeling disclosed by Lockhart et al. is encompassed by the claimed "directly labeling". The Examiner referred to page 7, lines 6-14 for support of this contention. Applicant assumes that the Examiner referred to page 7, lines 6-14 of Applicant's specification and not of Lockhart et al. ('27317). Applicant respectfully disagrees that the specification does not define "direct labeling" in Applicant's specification.

In Applicant's specification at page 7, starting on line 5, Applicant explains the difference between direct and indirect labeling. Direct labeling is a direct attachment while indirect labeling is an indirect attachment via hybridization with a complementary oligonucleotide having a label. See page 7, lines 5-20, of Applicant's specification. It is not the intent of the invention to be limited to particular labeling systems, such that a particular type of bond or attachment between the label and the probe be disclosed. It is sufficient for the purposes of the invention that directly labeling attaches a label directly to the probe while indirect labeling attaches a label to the probe indirectly via hybridization with a complement having a label. While the Examiner broadly interpreted "directly labeling" as including the ligation labeling disclosed by Lockhart et al., the Examiner still failed to show that a single prior art reference disclosed each and every claimed limitation in the arrangement as claimed in Claim 31. *In re Paulsen* (cited *supra*) and *Lindemann Maschinenfabrik GmbH v. American Hoist & Derrick Co.*, (cited *supra*).

Moreover, Claim 31 is dependent from Claim 30. Claim 30 recites a control probe and separately recites an oligonucleotide test probe each being attached in an array pattern of features. Lockhart et al. fail to disclose separately providing a control probe and an oligonucleotide test probe, especially wherein the control probes enhance detection of the features without interfering with oligomer test probe hybridization. Further, Lockhart et al. fail to disclose a control probe being directly labeled with a control label. Instead, Lockhart et al. disclose an oligonucleotide probe optionally having a constant region and a variable region, wherein a ligatable oligonucleotide having a label is ligated to the free terminus end of the oligonucleotide probe. This disclosure of Lockhart et al. fails to sufficiently enable and describe the claimed invention of Claims 30 and 31, such that the claimed invention would have been placed in the possession of a person skilled in the art (*In re Paulsen*, cited *supra*).

The Examiner had pointed out that the courts have stated that claims must be given their broadest reasonable interpretation consistent with the specification, citing *In re Morris*, 127 F. 3d 1048, 1054-55, 44 USPQ2d 1023, 1027-28 (Fed. Cir. 1997); In re Prater, 415 F. 2d 1393, 1404-05, 162 USPQ 541, 550-551 (CCPA 1969); *In re*

Zietz, 893 F. 2d 319, 321-22, 13 USPQ2d 1320, 1322 (Fed. Cir. 1989); and MPEP 2111. Therefore, the broadest reasonable interpretation of a 'control probe', that is consistent with Applicant's specification, is that defined in the specification at page 6, lines 1-7 and page 17, lines 10-18, for example. Since the definition in the specification does not go beyond that which is consistent with the definition of a control probe known in the art, the control probe claimed in Applicant's claims clearly is not the same as, or analogous to, the constant region disclosed by Lockhart et al. In fact, Lockhart et al. essentially admit that the constant region is not the same as a control probe, as is known in the art, at page 47, starting at line 25, where Lockhart et al. disclose using control probes in addition to the ligation reaction system comprising the oligonucleotide probe that optionally has a constant region and a variable region.

The same distinguishing features of the claimed invention mentioned above for Claim 30 and 31 also apply to the Examiner's contentions with respect to Claims 32-38. Lockhart et al. fail to disclose or suggest making an array with enhanced feature detectability comprising separately providing a control probe and an oligonucleotide test probe in an array pattern of features. Therefore, Lockhart et al. fail to disclose or suggest adding one end of a control probe to the substrate surface and indirectly labeling the control probe with the control label by hybridization with a control-specific target material that comprises the control label (Claim 32). Further, Lockhart et al. fail to disclose or suggest adding one end of a control probe to the substrate surface, directly labeling the control probe with a control probe label of the control label, and indirectly labeling the labeled control probe with the control target label of the control label by hybridization with a control-specific target material that comprises the control target label (Claim 33). Likewise, Lockhart et al. fail to disclose or suggest adding one end of a control probe to the substrate surface at the features, adding an oligomer test probe to the features, and indirectly labeling the control probe with the control label and the oligomer test probe with a test label by hybridization with a mixture comprising a labeled control-specific target material complementary to the control probe, and a labeled test target material complementary to the oligomer test probe, that respectively comprises the control label and the test label (Claim 34).

Further, Figures 13a - 13b, and page 71, line 1 to page 72, line 31 of Lockhart et al. ('27317) illustrate and describe an oligonucleotide probe that is bound at one end to a substrate surface. The oligonucleotide probe optionally comprises a constant region and a variable region. A complement to the constant region may be either hybridized or cross-linked to the constant region of the oligonucleotide probe. Lockhart et al. do not disclose or suggest that the complement comprises a control label. Instead, labels are added to the oligonucleotide probe via ligation with a ligatable oligonucleotide having a label (such as label B in Figure 13a, or the label in Figure 13b) and via hybridization of the variable region with a sample nucleic acid having a label (such as label A in Figure 13a). This disclosure is very different from the claimed invention in Claims 32-34.

With respect to Claims 35-36, Lockhart et al. do disclose adding an oligonucleotide probe and directly labeling the oligonucleotide probe with a ligatable oligonucleotide having a label, such as label B in Figure 13a and the label in Figure 13b (Claim 35); and indirectly labeling the oligonucleotide probe via hybridization with a sample nucleic acid having a label, such as label A in Figure 13a (Claim 36). However, Claims 35-36 are dependent from Claim 30 and includes all of the limitations of Claim 30. As mentioned above, Lockhart et al. fail to disclose or suggest Applicant's claimed control probe, separately adding the control probe and an oligomer test probe to a microarray, and especially a control probe that enhances detection of the features without interfering with oligomer test probe hybridization. Therefore, Lockhart et al. fail to disclose the invention of Claims 35-36 for at least the reasons set forth above for Claim 30.

With respect to Claims 37-38, for the same reasons set for above for Claim 30-36, Lockhart et al. do not disclose or suggest adding one end of a control probe to the substrate surface and separately adding a oligomer test probe to an opposite end of the control probe, such that the control probe is a stilt that extends between the oligonucleotide probe and the surface (Claim 37). Further, Lockhart et al. do not disclose or suggest adding one end of a control probe to the substrate surface and separately adding one end of a oligomer test probe to the surface, such that each

feature comprises the control probe and the oligomer test probe (Claim 38). In accordance with the invention, the oligomer test probe is attached within the features of the array pattern (as in Claims 30-38) whether by attaching one end to a free (opposite) end of the control stilt (as in Claim 37) or by attaching one end to the surface (as Claim 38).

Still further with respect to Claim 38, the Examiner contended that Lockhart et al. disclose a method comprising **"adding"** the one end to the surface because the constant region to which the oligonucleotide probe is attached is on the surface (emphasis is the Examiner's). Unfortunately, Applicant respectfully is at a loss with respect to what the Examiner intended by this contention.

In one sense, it appears that the Examiner is using the same reasoning in the rejection of Claims 37 and 38 where the limitations thereof contrast, thereby creating a contradiction. For example, if Applicant claims a control probe attached at one end to a substrate surface and a test probe attached at one end to the substrate surface, each separate probe is separately attached to the surface. There is no way that is the same as attaching a constant region of an oligonucleotide probe at one end to the substrate surface and attaching the variable region to the constant region, which is the Examiner's contention for Applicant's Claim 37. It is hardly appropriate to use the same facts to contend two contradictory things with respect to Claims 37 and Claim 38, in order to find more breadth in the teachings of Lockhart et al. than actually exists to one skilled in the art. The steps of adding to the surface that are claimed in Claim 38 are recited as separate or individual steps of adding to the surface.

In another sense, if the Examiner's contention was that the verb "adding" is too broad in Claim 38, Applicant would be willing to amend Claim 38 to recite "attaching" in both instances of "adding" therein, in order to expedite the prosecution of the application. However for the record, Applicant respectfully disagrees that the verb "adding" is too broad such that 'adding one end to the surface' somehow includes one end of the variable region being added to the constant region of the oligonucleotide probe of Lockhart et al., just because the constant region has one end

added to the surface. As mentioned above, Lockhart et al. fail to disclose or suggest providing a control probe and separately providing a test probe within the features of the array. Lockhart et al. disclose an oligonucleotide probe ***optionally*** comprising a constant region and a variable region. Applicant believes that the Examiner contended that the constant region is the same as Applicant's control probe and the variable region is the same as Applicant's test probe. However if that was correct, Lockhart et al. fail to disclose or illustrate adding the constant region to the surface and separately or independently adding the variable region to the surface in a method of making a microarray.

With respect to Claims 39, the Examiner contended that Lockhart et al. disclose presynthesizing the control probe and attaching one end of the presynthesized control probe to the substrate surface within each feature. The Examiner referred to page 47, lines 14-15 of Lockhart et al. for support of this contention. At page 47, lines 13-15, Lockhart et al. disclose that the optional constant domain of the probe oligonucleotide can be prepared *de novo* on the array or alternatively, may be prepared in a separate procedure and then coupled intact to the array. Claim 39 is ultimately dependent from Claim 30. It is respectfully submitted that Lockhart et al. ('27317) do not anticipate Claim 39 for at least the same reasons set forth above for Claim 30. As mentioned above, the constant domain or region of the oligonucleotide probe disclosed by Lockhart et al. is not the same as the control probe defined and claimed by Applicant. In particular, Lockhart et al. distinguish the constant domain of the oligonucleotide test probe from a control probe on page 47, starting on line 25 of Lockhart et al. ('27317), as being a reference or standard used in addition to the constant domain of the test probe. Therefore, Lockhart et al. essentially teach away from the Examiner's contention that the constant region of the test probe and Applicant's control probe are the same. The control probes disclosed by Lockhart et al. at page 47, starting on line 25, are the same as conventional control probes, which take up valuable real estate on the array, as described by Applicant at page 6, lines 1-7, for example. Therefore, contrary to that contended by the Examiner, Lockhart et al. fail to disclose the method of Applicant's invention according to Claim 39.

Claims 40-41 are ultimately dependent from Claim 39 and distinguish from the teachings of Lockhart et al. at least for the same reasons as set forth above for Claim 39.

With respect to Claim 44, the Examiner again contended that Lockhart et al. disclose providing a control probe comprising synthesizing the control probe *in situ* within each feature. The Examiner referred to page 47, line 13 of Lockhart et al. ('27317) for support of this contention. However as mentioned above, the control probe claimed by Applicant is not the same as the constant region or domain disclosed by Lockhart et al. The control probe of the present invention enhances feature detection without interfering with oligomer test probe hybridization. As mentioned above, Lockhart et al. essentially teach away from the constant region and a control probe being the same at page 47, starting at line 25, where Lockhart et al. separately disclose a control probe, which is a reference or standard, as mentioned above for Claim 39. Therefore, contrary to that contended by the Examiner, Lockhart et al. fail to disclose the method of Applicant's invention according to Claim 44.

Claims 45-48 are ultimately dependent from Claim 44 and distinguish from the teachings of Lockhart et al. at least for the same reasons as set forth above for Claim 44.

In light of the remarks above, Applicant respectfully requests reconsideration and withdrawal of the rejection of Claims 30-41 and 44-38 under 35 USC 102(b).

Claims 30-36, 38-40, 42, 44 and 47 were rejected under 35 USC 102(e) as being anticipated by Gentalen et al., U. S. Pat. No. 6,306,643 B1, filed 24 August 1998 ('643). The Examiner contended that Gentalen et al. disclose a method of making a microarray, as claimed in Applicant's Claim 30. It appears that the Examiner has analogized a common probe and a variable probe disclosed by Gentalen et al. at Column 14, line 59 to Column 15, line 4 to Applicant's control probe and oligomer test probe, respectively, to support this contention. Further, the Examiner contended that Gentalen et al. ('643) disclose at Column 11, lines 1-11 that a control probe is

associated with a control label that emits a control signal when excited by light. Applicant respectfully traverses this rejection.

Gentalen et al. ('643) disclose methods of using an array of pooled probes in genetic analysis. The array comprises arrays of polynucleotide probes having at least one pooled position. A typical array comprises a support having at least three discrete regions. At Column 14, starting at line 59, Gentalen et al. disclose an array of probes comprising a number of subarrays of pooled probe mixtures. The pools in each subarray have one common probe, and one variable probe. Collectively, the variable probes in a subarray constitute all probes of a given length. The common probes vary between the different subarrays. The common probes are chosen to be complementary to known regions of the target sequence that flank the regions to be sequenced. See Column 14, line 66 to Column 15, line 1. Gentalen et al. disclose as an example, if one is sequencing a chromosome, the common probes can be designed to be complementary to known markers distributed at fairly regular intervals throughout the chromosome. Having the common probes be complementary to known markers in the chromosome facilitates using arrays for sequence analysis of target samples that have recurring sequence segments throughout the target sequence that would otherwise limit the length of the target sequence that can be applied to the array or complicate data interpretation. See Gentalen et al. ('643) at Column 14, lines 45-58.

Clearly, the disclosure of using a common probe in Gentalen et al. ('643) is not the same as using a control probe, as is known in the art and as claimed by Applicant. Applicant refers the Examiner to page 6, lines 1-16 and page 17, lines 10-18 of Applicant's specification and further to page 47, starting on line 25, of Lockhart et al. ('27317) for support of the definition of a control probe in the art. A control probe is not, and does not function as, an oligomer test probe, and therefore, does not hybridize with test target sample and further, does not interfere with the hybridization of the oligomer test probe. See page 17, lines 16-18 of Applicant's specification. The control probe is used as a standard or reference in an assay to facilitate one or more of the manufacture of an array, the use of the array in an assay, and the analysis of the assay, to name a few for example. Further, Gentalen et al. are silent on using the

common probe for enhancing feature detection. Claim 30 now recites that the control probes enhance detection of the features without interfering with oligomer test probe hybridization.

The Examiner referred to Column 11, lines 1-11 to support a contention that Gentalen et al. disclose that the common probe is associated with a control label that emits a control signal. However, in Column 11, lines 1-11, Gentalen et al. actually disclose that labels can be incorporated into the test target sample during or after amplification. Moreover, in some methods, hybridization of the test target sample is compared with control nucleic acids. Optionally, such hybridizations can be performed simultaneously using different labels for the test target sample and the control sample. The control nucleic acid sample disclosed by Gentalen et al. at Column 11, lines 1-11 is different from and not analogous to the common probe included in each subarray. In fact, this disclosure by Gentalen et al. of using a control nucleic acid sample effectively teaches away from the Examiner's contention that the common probe in each subarray is the same as, or analogous to, a control probe.

For the purposes of the present invention, the control probe within the features of the array is associated with a control label that produces a signal. The signal emitted by the control label provides a reference signal that is detected independently of signals emitted from the oligomer test probes. In accordance with the present invention, the control probe provides enhanced feature position detection, such that reliance on the signal intensity of the hybridized test probes within a feature and/or the accuracy of probe placement manufacturing equipment used to make the array is reduced.

It is respectfully submitted that both the common probe and the variable probe disclosed by Gentalen et al. are designed to both hybridize to the test target sample for the purposes of determining the test target sequence. Each of the hybridized common probe and hybridized variable probe provides different information about the test target sequence. This clearly is not the same as Applicant's invention, as claimed in

Claim 30, and further as claimed in Claims 31-36, 38-40, 42, 44 and 47, which are ultimately dependent from Claim 30.

Again, the Examiner contended that the courts have stated that claims must be given their broadest reasonable interpretation consistent with the specification, citing *In re Morris*, 127 F. 3d 1048, 1054-55, 44 USPQ2d 1023, 1027-28 (Fed. Cir. 1997); In re Prater, 415 F. 2d 1393, 1404-05, 162 USPQ 541, 550-551 (CCPA 1969); *In re Zietz*, 893 F. 2d 319, 321-22, 13 USPQ2d 1320, 1322 (Fed. Cir. 1989) and MPEP 2111. Therefore as mentioned above, the broadest reasonable interpretation of a 'control probe', that is consistent with Applicant's specification, is that defined in the specification at page 6, lines 1-3 and page 17, lines 10-18, for example. Since the definition in the specification does not go beyond that which is consistent with the definition of a control probe known in the art, the control probe claimed in Applicant's claims clearly is not the same as, or analogous to, the common probe disclosed by Gentalen et al. when viewed by one skilled in the art.

Gentalen et al. ('643) fail to disclose each and every limitation of the claimed invention. (*In re Paulsen*, cited *supra*) as arranged in the claim *Lindemann Maschinenfabrik GmbH v. American Hoist & Derrick Co.*, cited *supra*), such that Gentalen et al. fail to enable and describe the claimed invention sufficiently to have placed it in possession of a person of ordinary skill in the art (*In re Paulsen*, cited *supra*, at 1673). Since the anticipation determination is viewed from one of ordinary skill in the art, there must be no difference between the claimed invention and the disclosure of Gentalen et al. ('643), as viewed by a person of ordinary skill in the field of the invention. *Scripps Clinic & Research Found. v. Genentech Inc.*, cited *supra*). It is respectfully submitted that the disclosure in Gentalen et al. ('643) is so different from the claimed invention that Gentalen et al. ('643) fail to place the presently claimed invention in the possession of one skilled in the art.

In light of the remarks above, reconsideration and withdrawal of the rejection of Claims 30-36, 38-40, 42, 44 and 47 under 35 USC 102(e) are respectfully requested.

Claims 42, 43 and 49 were rejected under 35 USC 103(a) as being unpatentable over Lockhart et al. ('27317). The Examiner contended that Lockhart et al. teach a method of making a microarray as claimed in Applicant's Claim 30, from which Claims 42, 43 and 49 are ultimately dependent. The Examiner further contended that it would be obvious to attach a presynthesized control probe to the surface and *in situ* synthesize a test probe to an opposite end of the control probe, at least due to the benefits of economy of time and labor, and that disclosed by Lockhart et al. at pages 59, 62, and 65. Applicant respectfully traverses this rejection.

Referring back to the remarks above regarding the rejection of Applicant's Claim 30 as being anticipated by the teachings of Lockhart et al., Lockhart et al. fail to disclose or suggest using a control probe, as defined and claimed by Applicant. Lockhart et al. disclose using an oligonucleotide probe that optionally includes a constant region and a variable region. Figure 13a illustrates that the constant region is attached at one end to the solid support. Lockhart et al. disclose that the order of the constant region and the variable region can be altered and multiple constant regions and variable regions may be included on the test probe. The control probe claimed by Applicant is not optional. Further, the control probe that is claimed by Applicant is always attached to the surface of the substrate; therefore there is no order that is alterable in the claimed invention. Still further, Lockhart et al. disclose using control probes at page 47, starting at line 25, as a separate entity in addition to the oligonucleotide test probe having the optional constant region and variable region. Therefore, Lockhart et al. effectively teach away from the Examiner's contention that the constant region of the oligonucleotide test probe is the same as, or analogous to, Applicant's claimed control probe.

It is well settled that it is improper to select particular teachings of a reference that support a rejection, while ignoring those teachings that teach away from the invention. *In re Mercer*, 185, USPQ 774, 778 (CCPA 1975); *In re Lunsford*, 53 CCPA 986, 357 F.2d 380, 148 USPQ 716 (1966). This approach "amounts in substance, to nothing more than a hindsight 'reconstruction' of the claimed invention by relying on isolated teachings of the prior art without considering the overall context

within which those teachings are presented. Without the benefit of appellant's disclosure, a person having ordinary skill in the art would not know what portions of the disclosure of the reference to consider and what portions to disregard as irrelevant, or misleading. See *In re Wesslau*, 53 CCPA 746, 353 F.2d 238, 147 USPQ 391 (1965)." *In re Mercer*, cited *supra*.

Therefore, the control probe claimed by Applicant in Claim 30, further characterized in Applicant's Claim 39, and also further characterized in Claims 42, 43 and 49 with respect to the oligomer test probe, is not disclosed or suggested by Lockhart et al. Therefore, the teachings of Lockhart et al. fail to make obvious the present invention according to Claims 42, 43 and 49.

In light of the remarks above, reconsideration and withdrawal of the rejection of Claims 42, 43 and 49 under 35 USC 103(a) are respectfully requested.

A Notice to Comply with Nucleic Acid Sequence Rules was included in the Examiner's Office Action. The Examiner pointed out that the application fails to comply with the requirements of 37 CFR 1.821 through 1.825 because the application contains sequence disclosures at page 24 that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). Applicant greatly appreciates the Examiner's notification and a period of time to reply thereto that is co-extensive with the time for reply to the pending Office Action. Applicant provides herewith under separate cover an initial Sequence Listing in computer readable form, a paper copy thereof along with a copy of the Notice to Comply and a Statement that the content of the computer readable form and the paper copy are the same and that no new matter has been added as required by 37 CFR 1.821. Consideration of the above-mentioned enclosed compliance items is respectfully requested.

In summary, Claims 1-84 were pending. Claims 1-29 and 50-84 were canceled, without prejudice, for being drawn to a non-elected invention. Claims 30-49 were rejected and a Notice that the application failed to comply with the requirements of 37 CFR 1.821-1.825 was included. Applicant has amended the Abstract, has amended

the specification to correct a minor typographical error, and has amended Claims 30-34, 36 and 38. The actual amendments to the Abstract, the specification and the Claims can be found in the attached Appendix that follows below. Further, the compliance items listed on the enclosed copy of the 'Notice To Comply With Requirements ... Nucleotide Sequence ... Disclosures' are enclosed for consideration. Claims 30-49, as amended herein, are in condition for allowance. It is respectfully requested that Claims 30-49 be allowed, and that the application be passed to issue at an early date.

Should the Examiner have any questions regarding the above, please contact Gordon M. Stewart, Attorney for Applicant, Registration No. 30,528 at Agilent Technologies, Inc., telephone number (650) 485-2386.

Respectfully submitted,
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The above-referenced attached Appendix follows after this page.

CERTIFICATE OF MAILING

I hereby certify that this correspondence, including the following attached Appendix, is being deposited with the United States Postal Service as first class mail in an envelope addressed to the Commissioner for Patents, Washington, D. C. 20231, on *September 9, 2002.*

Elizabeth E. Leitereg — 9-9-02
Elizabeth E. Leitereg — **Date**

APPENDIX

Part I, Abstract of the Disclosure

A marked-up version of the replacement Abstract that shows the amended text follows. Words that are added are underlined. Words that are deleted are enclosed in brackets.

A [microarray apparatus with enhanced feature detectability, a] method of making [the apparatus] a microarray apparatus with enhanced feature detectability [and methods for detecting features on the apparatus provide] provides for accurate detection of each feature location, regardless of the quality or quantity of signals from hybridized oligomer test probes. The [apparatus and methods comprise] method comprises separately providing a control probe or stilt and an oligomer test probe at each feature location on the microarray, such that each feature comprises a control probe and a test probe. The control probe comprises a sequence of nucleic acids unique to the control probe. [When the] The control probe is labeled with a label that emits a control signal [when excited by light, such as by a microarray scanner, the label from the control probe is detected separately, preferably in a separate control signal detection channel of the detection portion of the scanner. Thus, the microarray apparatus of labeled control probes can be evaluated non-destructively for quality control purposes before it is used for hybridization experiments]. [An] The oligomer test probe is labeled with a test label that emits a test signal distinguishable from the control signal. [is attached to each feature of the microarray, such that each feature comprises a control probe and a test probe. In one embodiment, the oligomer test probe is attached to one end of the control probe, such that the control probe acts as a stilt essentially extending the oligomer test probe away from the surface of the microarray. Thus, there can be a 1:1 correlation between the quantity of control probe and the quantity of oligomer test probe. After hybridization with experimental target and control-specific target materials,] When the microarray is hybridized and interrogated, [such that a] the control signal [indicative of]

indicates the location of each and every feature on the array [will be emitted] and [a] the test signal [indicative of] indicates the location of hybridized oligomer test probes [will be emitted. The signals are collected in separate channels of the scanning system. Thus, the location of dim or weak signals from hybridized test probes can be detected and/or located using the data collected from the control signals. Further, every feature on the microarray can be directly normalized for various signal trends (global or local) across the array].

Part II, Specification

A marked-up version of the second full paragraph on page 4 of the specification follows. Please amend page 4, second full paragraph, lines 11-17, of the specification as indicated in the following marked-up version. Words that are added are underlined. Words that are deleted are enclosed in brackets.

As mentioned above, the density of probes on a microarray chip is ever increasing so that more genes can be analyzed at one time and thus, saves sample and reduces costs. Achieving smaller and more compact arrays will depend heavily on the manufacturing equipment and processing. It should be appreciated that as probe arrays for gene analysis become more [density] densely packed, very small errors in probe placement more severely impact the accuracy of the analysis of the hybridization results.

A marked-up version of Table 1 on page 24 of the specification, between lines 16 and 21 thereof follows. Please amend Table 1, as follows, to conform to 37 CFR 1.821(d) and the enclosed Amendment to Direct Entry of Sequence Listing by adding a column for the sequence identifier number. Words that are added are underlined. Words that are deleted are enclosed within brackets. Pre-existing underlined words from the specification, as filed, are shown below in bold print instead of being underlined herein to avoid confusion only.

Table 1: Examples of Control Probe Sequences

Name	**Sequence**	SEQ. ID NO
Pro25G	atcatcgtagctggtcagtgtatcc	1
HCV48-24	acaggggagtgatctatggtggagt	2

Part III, Claims

A marked-up version of Claims 1-84 follows. Please amend Claims 30-34, 36 and 38, as follows. Please cancel nonelected Claims 1-29 and 50-84, without prejudice. Claims 35, 37 and 39-49 are not amended and are presented as originally filed. Words that are added are underlined. Words that are deleted are enclosed in brackets. Claim status is stated in parenthesis at the beginning of each claim.

1. (NONELECTED/CANCELED) A microarray apparatus with enhanced feature detectability comprising:

a control probe comprising a control sequence of nucleic acids attached at one end in an array pattern of features on a surface of a microarray substrate;

an oligomer test probe comprising a sequence of nucleic acids attached at each feature location, such that each feature comprises the control probe and the oligomer test probe; and

a control label associated with the control probe that emits a control signal when exposed to light that is unique to the control probe.

2. (NONELECTED/CANCELED) The apparatus of Claim 1, wherein the oligomer test probe is attached to an opposite end of the control probe at each feature location and the control probe is a control stilt extending between the oligomer test probe and the surface of the substrate.

3. (NONELECTED/CANCELED) The apparatus of Claim 1, wherein the oligomer test probe is attached at the surface of the microarray substrate.

4. (NONELECTED/CANCELED) The apparatus of Claim 1, wherein the oligomer test probe is associated with a test label, wherein the test label emits a test signal when exposed to light, the test signal being different from the control signal.

5. (NONELECTED/CANCELED) The apparatus of Claim 4, wherein the test label is attached to a test target sample and the oligomer test probe is associated indirectly with the test label by hybridization of the test target to the oligomer test probe upon exposure of the apparatus to the labeled test target sample.

6. (NONELECTED/CANCELED) The apparatus of Claim 4, wherein the detectability of each feature on the microarray substrate is enhanced upon interrogation with a microarray scanner by detecting the control signal at each feature regardless of the quality of the test label signal at each feature.

7. (NONELECTED/CANCELED) The apparatus of Claim 1, wherein each feature on the substrate is detected by detecting the control signal upon interrogation with the scanner for a non-destructive quality control evaluation of the apparatus.

8. (NONELECTED/CANCELED) The apparatus of Claim 1, wherein the control probe is associated directly with the control label.

9. (NONELECTED/CANCELED) The apparatus of Claim 8, wherein each feature on the substrate is detected by detecting the control signal upon interrogation with a microarray scanner for a non-destructive quality control evaluation of the apparatus.

10. (NONELECTED/CANCELED) The apparatus of Claim 1, wherein the control label is attached to a control-specific target material that is complementary to the control probe and the control probe is associated indirectly with the control label by hybridization upon exposure of the apparatus to the labeled control target material.

11. (NONELECTED/CANCELED) The apparatus of Claim 10, wherein the labeled control target is included in a hybridization solution comprising the labeled test target that is complementary to the oligomer test probe, such that upon exposure of the apparatus to the hybridization solution and then a microarray scanner, the control signal from the hybridized control probe provides reference data that can be normalized with test signal data from the hybridized oligomer test probes.

12. (NONELECTED/CANCELED) The apparatus of Claim 1, wherein the control label comprises a control probe label and a control target label, the control probe label is associated directly with the control probe, the control target label is associated directly with a control-specific target material that is complementary to the control probe, and wherein the control probe label emits a control probe signal and the control target label emits a control target signal that is different from the control probe signal.

13. (NONELECTED/CANCELED) The apparatus of Claim 12, wherein the labeled control probe is associated indirectly with the control target label by hybridization upon exposure of the apparatus to the labeled control target material, and wherein the control probe signal is detected in a control probe detection channel and the control target signal is detected in a separate control target detection channel of a microarray scanner upon interrogation of the hybridized apparatus with the scanner.

14. (NONELECTED/CANCELED) The apparatus of Claim 12, wherein each feature on the microarray is detectable upon interrogation with a microarray scanner for a non-destructive quality control evaluation by detecting the control probe signal before hybridization, and for locating hybridized oligomer test probes on each feature by detecting the control target signal after hybridization.

15. (NONELECTED/CANCELED) The apparatus of Claim 14, wherein the labeled control target is included in a hybridization solution comprising a labeled test

target that is complementary to the oligomer test probe, and wherein the control target signal from the hybridized control probe provides reference data that can be normalized with hybridization data from the hybridized oligomer test probes.

16. (NONELECTED/CANCELED) A microarray apparatus with enhanced feature detectability having an oligomer test probe attached in an array pattern of features on a substrate, the apparatus comprising:

a control sequence of nucleic acids attached at one end to a surface of the substrate at each feature location; and

a control label associated with the control sequence that emits a control signal when excited by a light.

17. (NONELECTED/CANCELED) The microarray of Claim 16, wherein the oligomer test probe is attached to an opposite end of the control sequence at each feature location, such that each feature comprises the control probe and the oligomer test probe.

18. (NONELECTED/CANCELED) The microarray of Claim 16, wherein the oligomer test probe is attached to the surface of the substrate at each feature location, such that each feature comprises the control probe and the oligomer test probe.

19. (NONELECTED/CANCELED) The microarray of Claim 16, wherein the control label is associated directly with the control sequence, such that upon interrogation with the microarray scanner the control signal is emitted from each feature.

20. (NONELECTED/CANCELED) The microarray of Claim 16, wherein a test label is attached to a test target sample, the test label emitting a test signal when excited by the light, the test signal being different from the control signal and separately detectable upon interrogation with a microarray scanner, and wherein the test label is associated indirectly with the oligomer test probe upon hybridization of the labeled test target to the oligomer test probe, such that upon interrogation with the

microarray scanner, the control sequence emits the control signal at each feature and the test signal is emitted from only those features having a hybridized test probe.

21. (NONELECTED/CANCELED) The microarray of Claim 20, wherein the control label comprises a control sequence label and a control target label, the control sequence label is associated directly with the control sequence, the control target label is attached to a control target material that is complementary to the control sequence, the control target label is associated indirectly with the labeled control sequence upon hybridization of the labeled control target to the labeled control sequence.

22. (NONELECTED/CANCELED) The microarray of Claim 20, wherein the control label is attached to a control target material that is complementary to the control sequence, and wherein the control label and the test label are associated indirectly with the control sequence and the oligomer test probe, respectively, upon hybridization of the labeled control target to the control sequence and the labeled test target to the oligomer test probe, such that upon interrogation with the microarray scanner, the hybridized control sequence emits the control signal at each feature.

23. (NONELECTED/CANCELED) A method of performing a non-destructive quality control evaluation on an array of features on a surface of a microarray substrate comprising the steps of:

providing a labeled control probe to each feature on the surface of the microarray substrate, the labeled control probe emitting a control signal when excited by a light;

interrogating the populated microarray substrate; and

evaluating data acquired from the interrogation before further use of the populated microarray substrate.

24. (NONELECTED/CANCELED) The method of performing of Claim 23, wherein the step of interrogating comprises the steps of:

scanning the microarray substrate with a light to excite each labeled control probe; and

detecting the control signal from the labeled control probe on each feature.

25. (NONELECTED/CANCELED) The method of performing of Claim 23, wherein the step of evaluating comprises the step of:

using the data acquired for modifying subsequent depositions.

26. (NONELECTED/CANCELED) The method of performing of Claim 25, further comprising the step of:

subsequently providing an oligomer test probe to each feature of the microarray substrate based on the acquired data, such that each feature comprises the labeled control probe and the oligomer test probe.

27. (NONELECTED/CANCELED) The method of performing of Claim 26, wherein the step of evaluating comprises the step of:

forwarding the data acquired to a user to assist the user in evaluation of hybridization test results.

28. (NONELECTED/CANCELED) The method of performing of Claim 23, wherein after the step of evaluating, further comprises the step of:

forwarding the data acquired to a user to assist the user in evaluation of hybridization test results.

29. (NONELECTED/CANCELED) The method of performing of Claim 23, further comprising the step of:

providing an oligomer test probe to each feature of the microarray substrate, such that each feature comprises the labeled control probe and the oligomer test probe, either before or after the step of interrogating.

30. (AMENDED) A method of making a microarray with enhanced feature detectability, the microarray having a microarray substrate, the method comprising the steps of:

providing a control probe in an array pattern of features on a surface of the microarray substrate, the control probe being attached to the surface in the array pattern, the control probe being [associated] directly or indirectly labeled with a control label that emits a control signal when excited by a light; and

providing an oligomer test probe to [each feature location] the features, the oligomer test probe being attached in the array pattern, such that [each feature comprises] the features comprise the control probe and the oligomer test probe, wherein the control probes enhance detection of the features without interfering with oligomer test probe hybridization.

31. (AMENDED) The method of making of Claim 30, wherein the step of providing the control probe comprises the steps of:

adding one end of the control probe to the surface of the substrate within [each feature] the features; and

directly labeling the control probe with the control label.

32. (AMENDED) The method of making of Claim 30, wherein the step of providing the control probe comprises the steps of:

adding one end of the control probe to the surface of the substrate within [each feature] the features; and

indirectly labeling [associating the control label to] the control probe with the control label by hybridization when exposed to a control-specific target material that comprises the control label.

33. (AMENDED) The method of making of Claim 30, wherein the step of providing the control probe comprises the steps of:

adding one end of the control probe to the surface of the substrate within [each feature] the features, and

directly labeling the control probe with a control probe label of the control label, the control probe label emitting a control probe signal of the control signal; and

indirectly [associating a control target label of the control label to] labeling the labeled control probe with a control target label of the control label by hybridization when exposed to a control-specific target material that comprises the control target label, the control target label emitting a control target signal of the control signal that is different from the control probe signal.

34. (AMENDED) The method of making of Claim 30, wherein the steps of providing the control probe and providing the oligomer test probe comprises the steps of:

adding one end of the control probe to the surface of the substrate at [each feature location] the features;

adding the oligomer test probe to [each feature] the features; and

indirectly [associating the control label to] labeling the control probe with the control label and [a test label to] the oligomer test probe with a test label by hybridization when exposed to a hybridization mixture comprising a labeled test target sample complementary to the oligomer test probe and a labeled control-specific target material complementary to the control probe, wherein the labeled [control] control-specific target material comprises the control label and the labeled test target sample comprises the test label.

35. The method of making of Claim 30, wherein the step of providing the oligomer test probe comprises the steps of:

adding the oligomer test probe to each feature of the substrate; and

directly labeling the oligomer test probe with a test label.

36. (AMENDED) The method of making of Claim 30, wherein the step of providing the oligomer test probe comprises the steps of:

adding an oligomer test probe to [each feature] the features of the substrate; and

indirectly [associating a test label with] labeling the oligomer test probe with a test label by hybridization when exposed to a test target material that comprises the test label.

37. The method of making of Claim 30, wherein the step of providing the control probe comprises the step of adding one end of the control probe to the surface of the microarray substrate; and the step of providing the oligomer test probes comprises the step of adding the oligomer test probe to an opposite end of the control probe, such that the control probe is a stilt that extends between the oligomer test probe and the surface, such that each feature comprises the control stilt and the oligomer test probe.

38. (AMENDED) The method of making of Claim 30, wherein the step of providing the control probe comprises the step of adding one end of the control probe to the surface of the microarray substrate; and the step of providing the oligomer test probe comprises the step of adding one end of the oligomer test probe to the surface of the substrate at [each feature location] the features, such that [each feature comprises] the features comprise the control probe and the oligomer test probe.

39. The method of making of Claim 30, wherein the step of providing the control probe comprises the steps of:

presynthesizing the control probe; and

attaching one end of the presynthesized control probe to the surface of the substrate within each feature.

40. The method of making of Claim 39, wherein the step of providing the oligomer test probe comprises the step of:

presynthesizing the oligomer test probe; and

attaching the presynthesized oligomer test probe within each feature.

41. The method of making of Claim 40, wherein the step of attaching the presynthesized oligomer test probe comprises attaching the presynthesized oligomer test probe to an opposite end of the presynthesized control probe.

42. The method of making of Claim 39, wherein the step of providing the oligomer test probe comprises the step of:

synthesizing the oligomer test probe *in situ* within each feature.

43. The method of making of Claim 42, wherein the *in situ* synthesized oligomer test probe is synthesized on an opposite end of the presynthesized control probe.

44. The method of making of Claim 30, wherein the step of providing the control probe comprises the step of:

synthesizing the control probe *in situ* on the surface of the substrate within each feature.

45. The method of making of Claim 44, wherein the step of providing the oligomer test probe comprises the step of:

presynthesizing the oligomer test probe; and

attaching the presynthesized oligomer test probe within each feature.

46. The method of making of Claim 45, wherein the step of attaching the presynthesized oligomer test probe comprises attaching the presynthesized test probe to an unattached end of the *in situ* synthesized control probe.

47. The method of making of Claim 44, wherein the step of providing the oligomer test probe comprises the step of:

synthesizing the oligomer test probe *in situ* within each feature.

48. The method of making of Claim 47, wherein the *in situ* synthesized oligomer test probe is synthesized on an unattached end of the *in situ* synthesized control probe.

49. The method of making of Claim 30, wherein the steps of providing the control probe and providing the oligomer test probe comprises the steps of:

presynthesizing the control probe;

attaching one end of the presynthesized control probe to the surface of the substrate within each feature; and

synthesizing the oligomer test probe *in situ* on an opposite end of the presynthesized control probe.

50. (NONELECTED/CANCELED) A method of detecting hybridized features on a microarray using a microarray scanner comprising the steps of:

providing a microarray having a microarray substrate that comprises:

a control probe attached at one end in an array pattern of features on a surface of the substrate; and

an oligomer test probe added to each feature location;

providing a control-specific target material complementary to the control probe, wherein the control target comprises a control target label that emits a control target signal when excited by a light; and

providing the microarray and the labeled control target material to a user to perform a hybridization assay with a test target sample.

51. (NONELECTED/CANCELED) The method of detecting hybridized features of Claim 50, wherein the control probe is directly associated with a control probe label that emits a control probe signal when excited by the light, the control probe signal being different from the control target signal.

52. (NONELECTED/CANCELED) The method of detecting hybridized features of Claim 51, wherein before the step of providing the microarray to a user, the

microarray is interrogated with scanning equipment to excite the control probe label and obtain quality control data based on the control probe signal, and the step of providing the microarray to a user further comprises providing the data to the user.

53. (NONELECTED/CANCELED) The method of detecting hybridized features of Claim 50, wherein the oligomer test probe is directly associated with a test label that emits a test signal when excited by the light, the test signal being different from the control target signal.

54. (NONELECTED/CANCELED) The method of detecting hybridized features of Claim 50, wherein after the step of providing the microarray to a user, further comprising the step of performing a hybridization assay on the microarray with the test target sample, such that the hybridized oligomer test probe is associated with a test label that emits a test signal when excited by the light, the test signal being different from the control target signal.

55. (NONELECTED/CANCELED) The method of detecting hybridized features of Claim 54, wherein after the step of performing the assay, further comprising interrogating the hybridized microarray with the microarray scanner to obtain assay results, the step of interrogating comprising collecting the control target signal detected in a control channel and collecting the test signal detected in a test channel that is separate from the control channel of a detection system of the scanner.

56. (NONELECTED/CANCELED) The method of detecting hybridized features of Claim 55, wherein after the step of interrogating, further comprising the step of transmitting data representing the all or part of the assay results.

57. (NONELECTED/CANCELED) The method of detecting hybridized features of Claim 56, wherein after the step of transmitting data, further comprising the step of receiving the data.

58. (NONELECTED/CANCELED) The method of detecting hybridized features of Claim 55, wherein the assay results are analyzed at a first location, the method further comprising communicating the assay results or a conclusion based on the assay results to a second location remote from the first location.

59. (NONELECTED/CANCELED) The method of detecting hybridized features of Claim 58, wherein the test target sample is obtained from a third location remote from the first location or the second location.

60. (NONELECTED/CANCELED) A method of locating hybridized features on a microarray using a microarray scanner, the microarray having oligomer test probes in an array pattern of features on a substrate, the oligomer test probes for hybridizing with a target sample under test at one or more features, the hybridized oligomer test probes being labeled with a test label that emits a test signal when excited with a light, the method comprising the steps of:

providing a control probe to a surface of the substrate at each feature location, such that each feature comprises the control probe and the oligomer test probe;

associating a control label with the control probe, the control label emitting a control signal when excited with the light, the control signal being different from the test signal; and

interrogating the microarray substrate with the microarray scanner to locate the hybridized oligomer test probes by detecting the control signals at each feature and separately detecting the test signals from the one or more features and correlating the detected signals.

61. (NONELECTED/CANCELED) The method of locating hybridized features of Claim 60, wherein the step of associating a control label comprises the step of directly labeling the control probe with a control probe label that emits a control probe signal when excited by the light.

62. (NONELECTED/CANCELED) The method of locating hybridized features of Claim 61, wherein the step of associating a control label further comprises the step of providing a control-specific target material complementary to the control probe, wherein the control target comprises a control target label that emits a control target signal when excited by the light, the control target signal being different from the control probe signal, the control target label being indirectly associated with the control probe upon hybridization with the control specific target material.

63. (NONELECTED/CANCELED) The method of locating hybridized features of Claim 60, wherein the step of associating a control label comprises the step of providing a control-specific target material complementary to the control probe, wherein the control target comprises a control target label that emits a control target signal when excited by the light, the control target signal being different from the control probe signal, the control target label being indirectly associated with the control probe upon hybridization with the control specific target material.

64. (NONELECTED/CANCELED) The method of locating hybridized features of Claim 63, wherein in the step of providing a control-specific target material, the control-specific target material is hybridized to the control probe at the time the oligomer test probes are hybridized to the test target sample.

65. (NONELECTED/CANCELED) The method of locating hybridized features of Claim 60, wherein the control probe is provided prior to the oligomer test probes, the oligomer test probes are attached to the control probes at each feature and the control probe acts as a stilt extending the oligomer test probe from the surface of the substrate.

66. (NONELECTED/CANCELED) The method of locating hybridized features of Claim 60, wherein in the step of interrogating, the microarray scanner has a separate channel for detecting the test signals from the hybridized oligomer test probes and a separate channel for detecting the control signal from the control probe.

67. (NONELECTED/CANCELED) The method of locating hybridized features of Claim 62, wherein in the step of interrogating, the microarray scanner has a test channel for detecting the test signals from the hybridized oligomer test probes, a separate control channel for detecting the control probe signal from the control probe, and another separate control channel for detecting the control target signal from the hybridized control probe.

68. (NONELECTED/CANCELED) A method of detecting features on a microarray with a microarray scanner, the microarray comprising a substrate having a surface, the method comprising the steps of:

providing a control probe to the substrate in an array pattern of features on the surface of the substrate, the control probe being associated with a control label that emits a control signal when exposed to a light; and

providing an oligomer test probe to each feature location, such that each feature comprises the control probe and the oligomer test probe;

interrogating the microarray with the microarray scanner to detect the control signal; and

evaluating data collected on the detected control signal.

69. (NONELECTED/CANCELED) The method of detecting features of Claim 68, wherein the oligomer test probe is associated with a test label that emits a test signal when exposed to the light, the test signal being different from the control signal.

70. (NONELECTED/CANCELED) The method of detecting features of Claim 69, wherein the step of interrogating comprises the steps of:

scanning the microarray substrate with a light to excite the control label and the test label; and

detecting the control signal from each feature in a control detection channel of the scanner; and

separately detecting the test signal in a separate test detection channel of the scanner.

71. (NONELECTED/CANCELED) The method of detecting features of Claim 68, wherein the control label is associated directly with the control probe.

72. (NONELECTED/CANCELED) The method of detecting features of Claim 71, wherein the step of interrogating comprises detecting the control signal at each feature location to obtain quality control data on the microarray.

73. (NONELECTED/CANCELED) The method of detecting features of Claim 69, wherein before the step of interrogating, the method further comprises the step of exposing the microarray to a hybridization solution comprising a target sample under test comprising the test label; and wherein the step of evaluating comprises determining characteristics of the hybridization between the oligomer test probe and the test target sample at each feature location.

74. (NONELECTED/CANCELED) The method of detecting features of Claim 73, the hybridization solution further comprises a control-specific target material complementary to the control probe, the control target comprising the control label, such that the control label and test label are indirectly associated with the control probe and the oligomer test probe, respectively, by hybridization.

75. (NONELECTED/CANCELED) The method of detecting features of Claim 74, wherein the step of interrogating comprises the steps of:

detecting the control signal from the hybridized control probe at each feature location;

detecting the test signals from the hybridized oligomer test probes; and

using the detected control signals as reference data to normalize with the detected test signals.

76. (NONELECTED/CANCELED) The method of detecting features of Claim 74, wherein the control label comprises a control probe label and a control target label, the control probe label being associated directly with the control probe, the control target label being indirectly associated with the control probe by hybridization, and the control target comprising the control target label, and wherein the control probe label emits a control probe signal and the control target label emits a control target signal that is different from the control probe signal, and wherein both the control probe signal and the control target signal are different from the test signal.

77. (NONELECTED/CANCELED) The method of detecting features of Claim 76, wherein the step of interrogating comprises the steps of:

scanning the microarray substrate with a light to excite the control labels and the test label; and

detecting the control probe signal in a control probe detection channel of a control channel of the scanner;

separately detecting the control target signal in a separate control target detection channel of the control channel; and

further separately detecting the test signal from the hybridized oligomer test probes in a separate test detection channel of the scanner.

78. (NONELECTED/CANCELED) The method of detecting features of Claim 76, further comprising the step of first interrogating the microarray with a microarray scanner before the step of exposing the microarray to a hybridization solution, wherein the step of first interrogating comprises detecting the control probe signal at each feature location to obtain quality control data on the microarray, and wherein after the step of exposing, the step of interrogating the hybridized microarray comprises the steps of:

detecting the control target signal from the hybridized control probe at each feature location;

detecting the test signals from the hybridized oligomer test probe; and

using the detected control target signals as reference data to normalize with the detected test signals.

79. (NONELECTED/CANCELED) A kit for evaluating a sample of a test target nucleic acid sequence comprising:

an apparatus comprising a microarray substrate, a control probe attached in an array pattern of features on a surface of the substrate, and an oligomer test probe attached at each feature location;

a control-specific target material complementary to the control probe, wherein the control target comprises a control target label that emits a control target signal; and

instructions for using the apparatus and control target material.

80. (NONELECTED/CANCELED) The kit of Claim 79, wherein the control probe comprises a control probe label that emits a control probe signal, the control probe signal being different from the control target signal.

81. (NONELECTED/CANCELED) The kit of Claim 80, wherein the instructions comprise quality data about the apparatus obtained by interrogation of the apparatus with a microarray scanner to evaluate the control probe signal at each feature location.

82. (NONELECTED/CANCELED) The kit of Claim 80, wherein the instructions comprise instructions for obtaining quality data about the apparatus from the control probe signals at each feature location before evaluating the test target sample.

83. (NONELECTED/CANCELED) The kit of Claim 79, wherein the oligomer test probe comprises a test probe label that emits a test probe signal, the test probe signal being different from the control target signal.

84. (NONELECTED/CANCELED) The kit of Claim 79, wherein the control probe is attached at one end to the surface of the substrate and the oligomer test probe is attached to an opposite end of the control probe at each feature location, such that the control probe is a stilt extending between the oligomer test probe and the surface of the substrate.

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to the Commissioner for Patents, Washington, D. C. 20231, on *September 9, 2002.*

Elizabeth E. Leitereg 9-9-02

Elizabeth E. Leitereg **Date**

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